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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,821	10/16/2003	Eric Wickstrom	W1133/20008	2530

3000 7590 07/26/2007

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-75,80,82,83 and 85-92* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,17-25,35-40,46,47,53,57-68,74 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80,82,83,85,86 and 88-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/14/2007 has been entered.

2. Claims 2, 76-79, 81, and 84 have been cancelled. Claims 5, 6,15, 17-25, 35-40, 46, 47, 53, 57-68, 74, and 84 have been withdrawn. Claims 89-92 are new.

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82, 83,85, 86, and 88-92 are under examination.

Double Patenting

3. Applicant is advised that should claim 83 be found allowable, claim 85 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 85, 86, and 88-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166, of record), in view of both Meade et al. (US Patent No. 6,713,046, of record) and Basu et al. (Bioconjugate Chem, 1997, 8: 481-488, of record).

Tomalia et al. teach a compound having the formula T-P-M, wherein P represents a dendrimer such as PMAM (i.e., polymeric diagnostic or therapeutic moiety, which is a branched oligomeric polychelant) or Starburst, M represents a carried material, such as PNA, T represents a targeting moiety that can be an antibody fragment such as Fab, Fab', and wherein M and T are associated with the dendrimer via the same or different linkers (claims 1, 4, 7-10, 34, 88, 89) (column 1, lines 45-50, column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60). Tomalia et al. teach that two or more dendrimers can be associated with each other (covalently bridged or through other associations) (claim 12) and that the dendrimers can comprise chelants, i.e., the diagnostic moiety comprises a plurality of chelants, wherein the chelants can be complexed with diagnostic metal ions

(claims 13 and 26) (column 3, lines 22-40, column 13, lines 5-11, column 19, lines 11-16, column 22, lines 1-29, column 45, lines 1-9,) and optionally can comprise additional agents that could be diagnostic metal ions, such as gadolinium (claims 4, 13, 14, 16, and 54) (column 1, lines 59-65, column 22, lines 15-35, column 88, Example 24, column 89, Table XI). Tomalia et al. teach that the compound can be used either *in vitro* or *in vivo* as a cancer therapeutic and diagnostic agents for noninvasive imaging and for transferring of genetic material, such as PNA into cells to block the production of specific proteins, i.e., Tomalia et al. teach a method of retaining a compound inside the cells for diagnostic or therapeutic purposes (claims 41-45, 48, 52, 69, 70, 73, 75, 90, 91) (column 28, lines 28-40, column 39, lines 25-30, column 54, lines 8-18, claim 32). For *in vivo* use, the compound can be administered into the portal vein, i.e., intravascular administration (claims 55 and 56) (column 54, lines 10-15). With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition (claims 83, 85, 86, and 92). With respect to the specific linkers (claims 3 and 88), the specific chelants (claims 26 and 27), or the specific PNA lengths (claim 29), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method (in the instant case, the linkers or the chelants) with the purpose of optimizing the results. Again, absent evidence to

the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA. It is noted that Tomalia et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, Tomalia et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Tomalia et al. do not teach a biodegradation cleavage site. Meade et al. teach a biodegradation cleavage site (claim 11) (column 14, lines 20-30). It would have been obvious to one of skill in the art, at the time the invention was made, to include a biodegradation cleavage site, as taught by Meade et al, with a reasonable expectation of success. The motivation to do so is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. One

of skill in the art would have been expected to have a reasonable expectation of success because Meade et al. teach the successful use of such sites.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 85, 86, and 88-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. (Molecular Therapy, 2001, 3: 491-499, of record).

The teachings of Tomalia et al., Meade et al., and Basu et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 85, 86, and 88-92. Tomalia et al., Meade et al., and Basu et al. do not teach an oncogene, wherein the oncogene is K-RAS (claims 32, 33, 72, and 82), nor do they specifically teach treating pancreatic cancer (claim 49). Nakano et al. teach gene therapy by using antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to use the compound and the method of Tomalia et al., Meade et al., and Basu et al., wherein the PNA is directed against K-*ras*, to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express K-*ras*, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would

have been motivated to do so because Nakano et al. teach that K-*ras* is over-expressed in many cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 85, 86, and 89-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180, of record), in view of both Liang et al. (Molecular Therapy, 2000, 3: 236-243, of record) and Basu et al.

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (claims 1, 3, 4, 29, 31, 32, 34, 51, 52, 72, 73, 83, 85, 86, and 89-92) (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript (claims 1, 30-32, 69, 71, 72, 80). Lewis et al. teach that cells expressing high levels of *bcl-2* internalize significantly more conjugate as compared to cells expressing low *bcl-2* levels, i.e., the presence of the conjugate inside the cells indicates over-

expression of the *bcl-2* transcript therefore a pathological state that is cancer (claims 41, 42, 48-51, 75, and 80) (p. 1178, column 2 bridging p. 1179). It is noted that Lewis et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, Lewis et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation.

Lewis et al. do not teach a targeting moiety capable of binding to a cell surface molecule (claims 1, 41, 89, and 90). Liang et al. teach enhancing therapeutic delivery to cells by receptor-mediated endocytosis (Abstract, p. 236, column 2). Liang et al. teach conjugation of transferring to a PNA capable of binding to plasmid DNA, wherein conjugation is via a disulfide bond linkage and wherein the conjugate is used to deliver plasmid DNA to the transferrin receptor on cell surface (p. 239, columns 1 and 2, p. 240, columns 1 and 2). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al. by replacing their peptide with the transferring of Liang et al., with a reasonable expectation of success. The motivation to do so is provided by Liang et al., who teach the utility of using ligands for enhanced delivery of therapeutics to specific sites via receptor-mediated endocytosis

(p. 241, column 1, second paragraph, p. 242, column 2, second paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such compositions can be successfully made and used. With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition (claims 83, 85, 86, and 92), the transfection buffer comprising the conjugate is a pharmaceutical composition. With respect to the specific linkers (claims 3 and 88), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitations of the of the target nucleic acid sequence comprising some or all of a consecutive sequence of bases in a RNA transcript and of the RNA transcript being heteronuclear or messenger RNA (claims 30, 31, 50, 51, 71, 72, and 80), these are inherent to a method using PNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 85, 86, and 89-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al.

The teachings of Lewis et al., Liang et al., and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 85, 86, and 89-92. Lewis et al., Liang et al., and Basu et al. do not teach K-RAS (claims 33 and 82). Nakano et al. teach gene transfer antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al., Liang et al., and Basu et al. by using a PNA directed against K-*ras* and use it in a method of delivering diagnostic and therapeutic agents to cancer cells over-expressing K-*ras*, such as colon and pancreatic cancer cells, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is ove-expressed in many cancer cells, including pancreatic cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 85, 86, and 88-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al.

taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al.

The teachings of Lewis et al., Liang et al., and Basu et al. are applied as above for claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 85, 86, and 88-92. The teachings of Tomalia et al. and Meade et al. are applied as above for claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 85, 86, and 88-92. Lewis et al., Liang et al., and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration (claims 7-14, 16, 26, 27, 43-45, 54-56, and 88). Tomalia et al. and Meade et al. teach these limitations (see above). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al., Liang et al., and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success. One of skill in the art would have been motivated to use the dendrimers of Tomalia et al. because the art teaches dendrimers as being very efficient in delivering agents to cells. The motivation to use a plurality of chelants is also provided by Tomalia et al., who teach that such compounds can be used to deliver multiple agents to cells. The motivation to use a biodegradation cleavage site is provided by Meade et al. who teach that such a site allows the drug (in the instant case, the PNA) to freely interact with its target. The limitation of intravascular administration is not innovative over the prior art. One of skill in the art would have been expected to have a reasonable expectation of success

because the art teaches the successful maker and use of such compositions. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Response to Arguments

10. Applicant traversed the instant rejections above on the grounds that knowledge of the invention did not exist in the prior art because the references cited by the Examiner do not provide the motivation for one of skill in the art to make or modify the applied art to reach the instant invention. In support for these arguments, Applicants enclosed a Rule 132 Declaration by Dr. Wickstrom. In his Declaration, Dr. Wickstrom submits that it is not enough to disclose single units forming the composition because the order of functional units in the composition of the invention is vital for the purpose of the composition entering the cell and binding to the nucleic acid target, as stated on p. 5 of the specification. Dr. Wickstrom argues that the compound of Tomalia et al., i.e., $(T)_e*(P)_x*(M)_y$ function contrarily to the compound of the present invention because the compound of Tomalia et al. permits binding to multiple neighboring cells via multiple T interactions on the surface of the dendrimer, preventing internalization of the compound into a single target cell, which in turn will prevent the binding of PNA to the nucleic acid inside the cell. Therefore, the compound of Tomalia et al. fails to teach or suggest the compound of the invention and one of skill in the art would not be motivated to use this compound to bind to the surface of a cell for internalization. Dr. Wickstrom argues that Meade et al. does not remedy the deficiencies of Tomalia et al. With respect to Lewis et al., Dr. Wickstrom argues that their peptide is designated for unspecific intracellular

delivery and therefore, their compound lacks specificity for cancer cells. With respect to Lianfg et al., Dr. Wickstrom submits that they teach transferring-PNA conjugate associated with plasmid DNA, wherein no cellular uptake is observed unless the conjugate was associated with polyethylenimine, that the toxicity of polyethylenimine teaches away from using the construct of Liang et al. in humans, and that their construct lacks the specificity provided by the instant invention because transferring is large, binds strongly to an ubiquitous receptor, and therefore, all cells would take up transferrin. Dr. Wickstrom argues that one of skill in the art would not be motivated to combine the references to achieve the instant composition with a reasonable expectation of success because such motivation is not present in the cited references and that the motivation cannot be "borrowed" from the current invention. Dr. Wickstrom submits that the invention is drawn to methods and compositions for non-invasive, effective, sensitive, and highly specific detection of gene expression *in vivo*, in a chosen cell, wherein the compositions are stable, non-toxic, and should not cause degradation of RNA, and that such an invention is not obvious over the prior art. Finally, Dr. Wickstrom argues that Applicants achieved surprising results and cites a number of papers in support for this argument, wherein the surprising results were obtained from the design of dual specificity hybridization probes that require receptor-specific uptake, followed by mRNA-specific hybridization and retention in cancer cells. Dr. Wickstrom submits that one of skill in the art did not anticipate Applicants' design and therefore the positive results were unexpected.

Applicant's arguments are acknowledged, however, the rejections are maintained for the following reasons:

Dr. Wickstrom argues that the compound of Tomalia et al., i.e., $(T)_e*(P)_x*(M)_y$ function contrarily to the compound of the present invention because the compound of Tomalia et al. permits binding to multiple neighboring cells via multiple T interactions on the surface of the dendrimer, preventing internalization of the compound into a single target cell, which in turn will prevent the binding of PNA to the nucleic acid inside the cell. However, Applicant did not submit any evidence that this is indeed the case. This argument is not found persuasive because Tomalia et al. clearly teach that in the formula $(T)_e*(P)_x*(M)_y$, wherein T is the targeting moiety (or target director), "e" is preferably 1, i.e., the dendrimer comprises a single targeting moiety (column 22, lines 30-35); therefore, the compound cannot bind to multiple cells via multiple T interaction, because there are not multiple T moieties. Additionally, Tomalia et al. teach (column 52):

> "Incorporation of target directors into the dendrimer-genetic material complex not only directs the complex to a desired cell, but may also enhance transfection of cells with the target moiety.
>
> The use of target director is very important *in vivo* transfection of genetic material into cells. DEAE-dextran, while not toxic for purpose of *in vitro* use, would not be suitable for *in vivo* use as a transfection enhancer. Dendrimer-genetic material complexes, with or without an enhancing agent, do not significantly transfect cells in the presence of serum. A target director, promoting binding of the genetic amterial-dendrimer complex to specifically targeted cells, facilitates transfection of genetic material into those cells even in the presence of serum."

By reading Tomalia et al., one of skill in the art would have known and would have been be motivated to use their compound to specifically deliver PNA to target

cells. The argument that the combination of Tomalia et al. and Meade et al. requires the eradication of the intended function of the references is not supported by evidence and it is not clear why Applicant presented such an argument.

With respect to Lewis et al. and Liang et al., it is noted that Applicant's arguments are directed against the references individually, while the rejection is based on the combination of the above references; one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Lewis et al. teach using a peptide that is not cell-specific. Therefore, one of skill in the art would have been motivated to modify the compound of Lewis et al. by replacing their peptide with a more specific ligand for a cell surface receptor (therefore art provides the motivation to combine and the motivation is not "borrowed" from the current invention). Liang et al. teach such a ligand. The ligand of Liang et al. (i.e., transferrin) is only an example; the important fact is that the concept of cell targeting is taught by the prior art. One of skill in the art would have been aware of the existence of other more specific ligands that could be used in the method of Lewis et al. Moreover, the claims broadly recite the genus of a targeting moiety capable of binding to a cell surface molecule, and the transferrin of Liang et al. anticipates the claimed genus. With respect to the argument that the polyethylenimine taught by Liang et al. is toxic *in vivo*, it is noted that the combined references do not require the use of polyethylenimine; the combined references teach a composition comprising DOTA, PNA, and transferrin.

With respect to the papers provided by the Applicant in support for the argument that the claimed design leads to surprising results, it is noted that such a conclusion is improper because the provided references do not teach an experiment comparing the claimed arrangement with the arrangement of Tomalia et al. or Lewis et al. Therefore, there is no evidence in the art or specification that the claimed arrangement results in unexpected properties, as compared to the arrangement taught by Tomalia et al. and Lewis et al. It is noted that Applicant provided no evidence that positive results could not be obtained with the arrangement of Tomalia et al. or Lewis et al. Moreover, although Tomalia et al. or Lewis et al. do not teach the specific arrangement recited in the instant claims (i.e., X-L1-P-L2-T), they do teach a composition comprising all components necessary for this arrangement, wherein the composition has the same properties as the claimed composition, i.e., the claimed arrangement does not result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. For these reasons, Dr. Wickstrom's argument that one of skill in the art did not anticipate Applicants' design and therefore the positive results were unexpected is not found persuasive. The claimed arrangement was *prima facie* obvious over the prior art, i.e., the positive results were not unexpected.

Based on all of the above, the combined references teach a composition and a method that is not different from the instant method and composition.

11. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system; contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Joe Woitach
AU1633